PRODUCT INFORMATION

AGENERASE®

(amprenavir)

Oral Solution

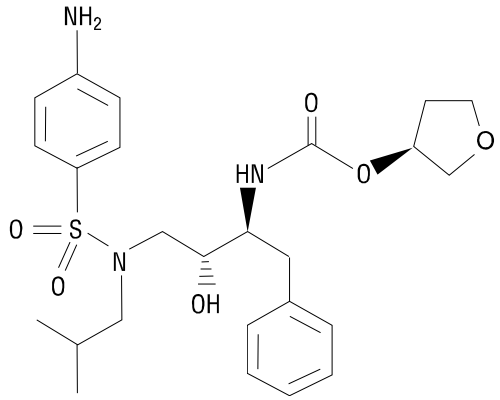
PATIENT INFORMATION INCLUDED

AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV RNA or disease progression with AGENERASE.

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CONTRAINDICATIONS AND WARNINGS).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

DESCRIPTION: AGENERASE (amprenavir) is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3*S*)-tetrahydro-3-furyl *N*-[(1*S*,2*R*)-3-(4-amino-*N*-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{35}N_3O_6S$ and a molecular weight of 505.64. It has the following structural formula:



Amprenavir is a white to cream-colored solid with a solubility of approximately 0.04 mg/mL in water at 25°C.

AGENERASE Oral Solution is for oral administration. One milliliter (1 mL) of AGENERASE Oral Solution contains 15 mg of amprenavir in solution and the inactive ingredients acesulfame potassium, artificial grape bubblegum flavor, citric acid (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavor, polyethylene glycol 400 (PEG 400) (170 mg), propylene glycol (550 mg), saccharin sodium, sodium chloride, and sodium citrate (dihydrate). Solutions of sodium hydroxide and/or diluted hydrochloric acid may have been added to adjust pH. Each mL of AGENERASE Oral Solution contains 46 IU vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE Oral Solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg per day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

MICROBIOLOGY:

Mechanism of Action: Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity *in Vitro*: The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC_{50}) of amprenavir ranged from 0.012 to 0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 mcg/mL). Amprenavir exhibited synergistic anti-HIV-1 activity in

combination with abacavir, zidovudine, didanosine, or saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir, and ritonavir *in vitro*. These drug combinations have not been adequately studied in humans. The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in vitro* and were also obtained from patients treated with amprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions M46I/L, I47V, I50V, I54L/V, and I84V as well as mutations in the viral protease p1/p6 cleavage site. Phenotypic analysis of HIV-1 isolates from some patients on amprenavir monotherapy for 8 to 12 weeks showed a 5- to 10-fold decrease in susceptibility to amprenavir *in vitro* compared to baseline. Phenotypic analysis of HIV-1 isolates from 28 patients treated with amprenavir in combination with zidovudine and lamivudine for 16 to 36 weeks identified isolates from 6 patients that exhibited a 5- to 11-fold decrease in susceptibility to amprenavir *in vitro* compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored amprenavir-associated mutations. The clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy has not been established.

Cross-Resistance: Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. The potential for protease inhibitor cross-resistance in HIV-1 isolates from amprenavir-treated patients has not been fully evaluated.

CLINICAL PHARMACOLOGY:

Pharmacokinetics in Adults: The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150 to 1200 mg and multiple oral doses of 300 to 1200 mg twice daily.

Absorption and Bioavailability: Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (t_{max}) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1200 mg were slightly greater than dose proportional. Increases in AUC

were dose proportional after 3 weeks of dosing with doses from 300 to 1200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir 1200 mg b.i.d. for 3 weeks to HIV-infected subjects are shown in Table 1.

Table 1: Average (%CV) Pharmacokinetic Parameters
After 1200 mg b.i.d. of Amprenavir Capsules (n = 5)

C_{max} (mcg/mL)	t_{max} (hours)	AUC_{0-12} (mcg•h/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
5.36 (62%)	1.9 (51%)	18.5 (63%)	1.54 (63%)	0.28 (52%)	31 (132%)

The relative bioavailability of AGENERASE Capsules and Oral Solution was assessed in healthy adults. AGENERASE Oral Solution was 14% less bioavailable compared to the capsules.

Effects of Food on Oral Absorption: The relative bioavailability of AGENERASE Capsules was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate). Administration of a single 1200-mg dose of amprenavir in the fed state compared to the fasted state was associated with changes in C_{max} (fed: 6.18 ± 2.92 mcg/mL, fasted: 9.72 ± 2.75 mcg/mL), t_{max} (fed: 1.51 ± 0.68, fasted: 1.05 ± 0.63), and $AUC_{0-\infty}$ (fed: 22.06 ± 11.6 mcg•h/mL, fasted: 28.05 ± 10.1 mcg•h/mL). AGENERASE may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION).

Distribution: The apparent volume of distribution (V_z/F) is approximately 430 L in healthy adult subjects. *In vitro* binding is approximately 90% to plasma proteins. The high affinity binding protein for amprenavir is $alpha_1$-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: Amprenavir is metabolized in the liver by the cytochrome P450 CYP3A4 enzyme system. The two major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

AGENERASE Oral Solution contains a large amount of propylene glycol, which is hepatically metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Alcohol dehydrogenase (ADH) is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults. Additionally, certain patient groups (females, Asians, Eskimos, Native Americans) may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1 to 10.6 hours.

Special Populations: ***Hepatic Insufficiency:*** AGENERASE Oral Solution is contraindicated in patients with hepatic failure.

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with hepatic impairment. AGENERASE Capsules have been studied in adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•h/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•h/mL). The $AUC_{0-\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0-\infty}$: 38.66 ± 16.08 mcg•h/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0-\infty}$: 12.00 ± 4.38 mcg•h/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: AGENERASE Oral Solution is contraindicated in patients with renal failure.

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. Additionally, because metabolites of the excipient propylene glycol in AGENERASE Oral Solution may alter acid-base balance, patients with renal impairment should be monitored for potential adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with renal impairment. The impact of renal impairment on amprenavir

elimination has not been studied. The renal elimination of unchanged amprenavir represents <3% of the administered dose.

Pediatric Patients: AGENERASE Oral Solution is contraindicated in infants and children below 4 years of age (see CONTRAINDICATIONS and WARNINGS).

The pharmacokinetics of amprenavir have been studied after either single or repeat doses of AGENERASE Capsules or Oral Solution in 84 pediatric patients. Twenty HIV-1-infected children ranging in age from 4 to 12 years received single doses from 5 mg/kg to 20 mg/kg using 25-mg or 150-mg capsules. The C_{max} of amprenavir increased less than proportionally with dose. The $AUC_{0-\infty}$ increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore **AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis.**

Table 2: Average (%CV) Pharmacokinetic Parameters in Children Ages 4 to 12 Years Receiving 20 mg/kg b.i.d. or 15 mg/kg t.i.d. of AGENERASE Oral Solution

Dose	n	C_{max} (mcg/mL)	t_{max} (hours)	AUC_{ss}* (mcg•h/mL)	C_{avg} (mcg/mL)	C_{min} (mcg/mL)	CL/F (mL/min/kg)
20 mg/kg b.i.d.	20	6.77 (51%)	1.1 (21%)	15.46 (59%)	1.29 (59%)	0.24 (98%)	29 (58%)
15 mg/kg t.i.d.	17	3.99 (37%)	1.4 (90%)	8.73 (36%)	1.09 (36%)	0.27 (95%)	32 (34%)

*AUC is 0 to 12 hours for b.i.d. and 0 to 8 hours for t.i.d., therefore the C_{avg} is a better comparison of the exposures.

Geriatric Patients: The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

Gender: The pharmacokinetics of amprenavir do not differ between males and females. Females may have a lower amount of alcohol dehydrogenase compared with males and may be at increased risk of propylene glycol-associated adverse events; no data are available on propylene glycol metabolism in females.

Race: The pharmacokinetics of amprenavir do not differ between Blacks and non-Blacks. Certain ethnic populations (Asians, Eskimos, and Native Americans) may be at increased risk of propylene glycol-associated adverse events because of alcohol dehydrogenase polymorphisms; no data are available on propylene glycol metabolism in these groups.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.

Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with amprenavir capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C_{max}, and C_{min} are summarized in Table 3 (effect of other drugs on amprenavir) and Table 4 (effect of amprenavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS.

Table 3: Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug

Co-administered Drug	Dose of Coadministered Drug	Dose of AGENERASE	n	% Change in **Amprenavir** Pharmacokinetic Parameters* (90% CI)		
				C_{max}	AUC	C_{min}
Abacavir	300 mg b.i.d. for 3 weeks	900 mg b.i.d. for 3 weeks	4	↑47 (↓15 to ↑154)	↑29 (↓18 to ↑103)	↑27 (↓46 to ↑197)
Clarithromycin	500 mg b.i.d. for 4 days	1200 mg b.i.d. for 4 days	12	↑15 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
Indinavir	800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole	400 mg single dose	1200 mg single dose	12	↓16 (↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	⇔ (↓17 to ↑9)	⇔ (↓15 to ↑14)	NA
Nelfinavir	750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	⇔ (↓19 to ↑47)	↑189 (↑52 to ↑448)
Rifabutin	300 mg q.d. for 10 days	1200 mg b.i.d. for 10 days	5	⇔ (↓21 to ↑10)	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
Rifampin	300 mg q.d. for 4 days	1200 mg b.i.d. for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
Saquinavir	800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
Zidovudine	300 mg single dose	600 mg single dose	12	⇔ (↓5 to ↑24)	↑13 (↓2 to ↑31)	NA

*Based on total-drug concentrations.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study.

Table 4: Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir

Co-administered Drug	Dose of Co-administered Drug	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI)		
				C_{max}	AUC	C_{min}
Clarithromycin	500 mg b.i.d. for 4 days	1200 mg b.i.d. for 4 days	12	↓10 (↓24 to ↑7)	⇔ (↓17 to ↑11)	⇔ (↓13 to ↑20)
Ketoconazole	400 mg single dose	1200 mg single dose	12	↑19 (↑8 to ↑33)	↑44 (↑31 to ↑59)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	⇔ (↓17 to ↑3)	⇔ (↓11 to 0)	NA
Rifabutin	300 mg q.d. for 10 days	1200 mg b.i.d. for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifampin	300 mg q.d. for 4 days	1200 mg b.i.d. for 4 days	11	⇔ (↓13 to ↑12)	⇔ (↓10 to ↑13)	ND
Zidovudine	300 mg single dose	600 mg single dose	12	↑40 (↑14 to ↑71)	↑31 (↑19 to ↑45)	NA

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study; ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors: The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

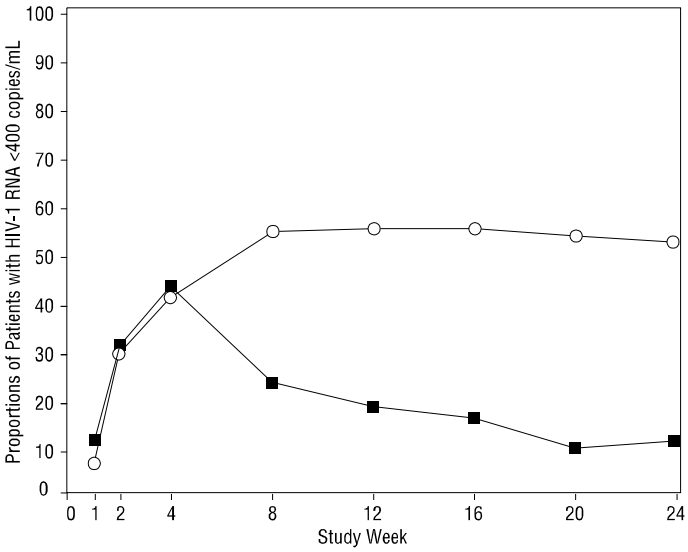
For information regarding clinical recommendations, see PRECAUTIONS: Drug Interactions.

INDICATIONS AND USAGE: AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV RNA or disease progression with AGENERASE (see Description of Clinical Studies).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

Description of Clinical Studies: ***Therapy-Naive Adults:*** PROAB3001, an ongoing, randomized, double-blind, placebo-controlled, multicenter study, compared treatment with AGENERASE Capsules (1200 mg twice daily) plus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) versus lamivudine (150 mg twice daily) plus zidovudine (300 mg twice daily) in 232 patients, median age 37 years (range 18 to 63 years), 75% Caucasian, 89% male, with a median CD4 cell count of 416 cells/mm^3 (range 139 to 1800 cells/mm^3) and a median plasma HIV-1 RNA of 4.67 $\log_{10}$ copies/mL (range 3.06 to 6.31 $\log_{10}$ copies/mL) at baseline. Through 24 weeks of therapy, there was no significant difference in the median CD4 cell count between the treatment arms. Figure 1 shows the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL through 24 weeks.

Figure 1: Virologic Response Through Week 24, PROAB3001[1,2]



[1]Roche AMPLICOR HIV-1 MONITOR assay.
[2]Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

HIV-1 RNA status and reasons for discontinuation of randomized treatment at 24 weeks are summarized (Table 5).

Table 5: Outcomes of Randomized Treatment Through Week 24 (PROAB3001)

Outcome	AGENERASE (n = 116)	Placebo (n = 116)
HIV RNA <400 copies/mL*	53%	11%
HIV RNA ≥400 copies/mL[†,‡]	13%	62%
CDC Class C event[‡]	0%	0%
Discontinued due to adverse events[‡]	15%	3%
Discontinued due to other reasons[‡,§]	19%	22%
On treatment with missing HIV RNA value[‡]	0%	1%
TOTAL	100%	100%

*Corresponds to rates at Week 24 in Figure 1.

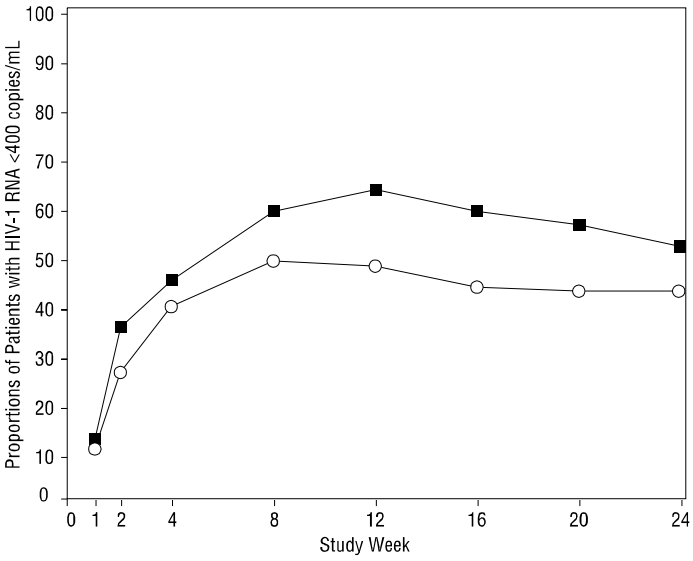
[†]Includes discontinuations due to virological failure at or before Week 24.

[‡]Treatment failure in the analysis.

[§]Consent withdrawn, lost to follow-up, and protocol violation.

Therapy-Experienced Adults: PROAB3006, an ongoing, randomized, open-label multicenter study, compared treatment with AGENERASE Capsules (1200 mg twice daily) plus NRTIs versus indinavir (800 mg every 8 hours) plus NRTIs in 504 NRTI- and non-nucleoside reverse transcriptase inhibitor- (NNRTI) experienced, protease inhibitor-naive patients, median age 37 years (range 20 to 71 years), 72% Caucasian, 80% male, with a median CD4 cell count of 399 cells/mm^3 (range 9 to 1706 cells/mm^3) and a median plasma HIV-1 RNA level of 3.93 $\log_{10}$ copies/mL (range 2.60 to 7.01 $\log_{10}$ copies/mL) at baseline. Through 24 weeks of therapy, there was a smaller increase in median CD4 cell count from baseline for the amprenavir group than for the indinavir group. Figure 2 shows the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL through 24 weeks.

Figure 2: Virologic Response Through Week 24, PROAB3006[3,4]



[3]Roche AMPLICOR HIV-1 MONITOR assay.
[4]Discontinuations and missing data were considered as HIV-1 RNA ≥400 copies/mL.

HIV-1 RNA status and reasons for discontinuation of randomized treatment at 24 weeks are summarized (Table 6).

Table 6: Outcomes of Randomized Treatment Through Week 24 (PROAB3006)

Outcome	AGENERASE (n = 254)	Indinavir (n = 250)
HIV RNA <400 copies/mL*	43%	53%
HIV RNA ≥400 copies/mL[†,‡]	22%	18%
CDC Class C event[‡]	<1%	2%
Discontinued due to adverse events[‡]	16%	8%
Discontinued due to other reasons[‡,§]	14%	12%
On treatment with missing HIV RNA value[‡]	4%	7%
TOTAL	100%	100%

*Corresponds to rates at Week 24 in Figure 2.

[†]Includes discontinuations due to virological failure at or before Week 24.

[‡]Treatment failure in the analysis.

[§]Consent withdrawn, lost to follow-up, and protocol violation.

CONTRAINDICATIONS: Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see WARNINGS and PRECAUTIONS).

AGENERASE also should not be administered concurrently with astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, midazolam, and triazolam. Although these drugs have not been specifically studied, coadministration may result in competitive inhibition of metabolism of these products and may cause serious or life-threatening adverse events. (See WARNINGS for agents whose coadministration may result in competitive inhibition of metabolism but for which concentration monitoring is recommended.)

AGENERASE is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product.

WARNINGS: Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and PRECAUTIONS).

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (Asians, Eskimos, Native Americans) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol metabolism in these groups (see CLINICAL PHARMACOLOGY: Special Populations: Gender and Race).

If patients require treatment with AGENERASE Oral Solution, they should be monitored closely for propylene glycol-associated adverse events, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis. Patients should be switched from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation.

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with AGENERASE (see CONTRAINDICATIONS).

Rifampin should not be used in combination with amprenavir because it reduces plasma concentrations and AUC of amprenavir by about 90%.

Concomitant use of AGENERASE and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including AGENERASE, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to AGENERASE or to the class of protease inhibitors.

Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving amprenavir. Coadministration of AGENERASE with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS: Drug Interactions and Information for Patients, and the complete prescribing information for sildenafil).

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with AGENERASE (see ADVERSE REACTIONS).

Acute hemolytic anemia has been reported in a patient treated with AGENERASE.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS:

General: AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY: Pediatric Patients and CONTRAINDICATIONS).

Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown. Patients with a known sulfonamide allergy should be treated with caution.

AGENERASE is principally metabolized by the liver; therefore caution should be exercised when administering this drug to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

Formulations of AGENERASE provide high daily doses of vitamin E (see Information for Patients, DESCRIPTION, and DOSAGE AND ADMINISTRATION). The effects of long-term, high-dose vitamin E administration in humans is not well characterized and has not been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption.

Patients with Hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Fat Redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving protease inhibitors. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Resistance/Cross-Resistance: Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have on the activity of subsequently administered protease inhibitors (see MICROBIOLOGY).

Information for Patients: A Patient Package Insert (PPI) for AGENERASE Oral Solution is available for patient information.

AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole. AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

Patients treated with AGENERASE Capsules should be cautioned against switching to AGENERASE Oral Solution because of the increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Women, Asians, Eskimos, or Native Americans, as well as patients who have hepatic or renal insufficiency, should be informed that they may be at increased risk of adverse events from the large amount of propylene glycol in AGENERASE Oral Solution.

Patients should be informed that AGENERASE is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of AGENERASE (amprenavir) are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with AGENERASE can reduce the risk of transmitting HIV to others through sexual contact.

Patients should remain under the care of a physician while using AGENERASE. Patients should be advised to take AGENERASE every day as prescribed. AGENERASE must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their doctor if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.

AGENERASE may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

Patients taking antacids (or didanosine) should take AGENERASE at least 1 hour before or after antacid (or didanosine) use.

Patients should be advised that drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctor.

Patients receiving hormonal contraceptives should be instructed that alternate contraceptive measures should be used during therapy with AGENERASE.

High-fat meals may decrease the absorption of AGENERASE and should be avoided. AGENERASE may be taken with meals of normal fat content.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of AGENERASE exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Drug Interactions.

AGENERASE is an inhibitor of cytochrome P450 CYP3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and WARNINGS).

Table 7: Drug Interactions with AGENERASE

Should Not Be Coadministered	
Drug Class	Drug Within Class Not To Be Coadministered
Alcohol dependence treatment	Disulfiram (do not administer with AGENERASE Oral Solution)
Antibiotics	Metronidazole (do not administer with AGENERASE Oral Solution)
Antihistamines	Astemizole
Antimycobacterials	Rifampin*
Benzodiazepines	Midazolam, triazolam
Cardiovascular	Bepridil
Ergot derivatives	Dihydroergotamine, ergotamine
GI motility agents	Cisapride

*****Decreases plasma concentrations of amprenavir and should not be coadministered as it is likely to reduce antiviral activity.

Coadministration Requires Concentration Monitoring	
Drug Class	Drug Within Class to Monitor
Antiarrhythmics	Amiodarone, lidocaine (systemic), quinidine
Anticoagulants	Warfarin*
Antidepressants	Tricyclic antidepressants

*Monitor INR (International Normalized Ratio).

Dosage Adjustment Required	
Drug Class	Drug Within Class Requiring a Dosage Adjustment
Antimycobacterials	Rifabutin (reduce dose to at least half that recommended)*

*A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin.

Other Potentially Significant Drug Interactions	
Anticonvulsants: phenobarbital, phenytoin, carbamazepine	Induce CYP3A4 and may decrease amprenavir concentrations.
Cholesterol-lowering agents: atorvastatin, cerivastatin, lovastatin, pravastatin, and simvastatin	May have their serum concentrations increased by AGENERASE, which could increase their activity or toxicity (see WARNINGS).
Erectile dysfunction agents: sildenafil	Expected to substantially increase sildenafil concentrations (consult sildenafil prescribing information for dose reduction of sildenafil in patients receiving ritonavir).
Other: St. John's wort	May decrease amprenavir concentrations.

Antimycobacterials: Rifampin: Rifampin should not be used in combination with amprenavir since it reduces plasma concentrations and AUC of amprenavir by about 90%.

Rifabutin: Coadministration of amprenavir with rifabutin results in a 15% decrease in amprenavir plasma AUC and a 193% increase in rifabutin plasma AUC. A dosage reduction of rifabutin to at least half the recommended dose is required when AGENERASE and rifabutin are coadministered (see CLINICAL PHARMACOLOGY: Drug Interactions). A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin.

Other Potentially Significant Drug Interactions: Other medications that interact at CYP3A4, either as substrates, inhibitors, or inducers of the enzyme, could have potential interactions when used concomitantly. The clinical significance of these potential interactions is unknown and has not been studied.

Antibiotics: Dapsone and erythromycin may have their plasma concentrations increased by AGENERASE. Erythromycin may also increase amprenavir serum concentrations.

Antifungals: Itraconazole may have its plasma concentrations increased by AGENERASE. Itraconazole may increase serum concentrations of amprenavir.

Benzodiazepines: Alprazolam, clorazepate, diazepam, and flurazepam may have their serum concentrations increased by AGENERASE, which could increase their activity.

Calcium Channel Blockers: Diltiazem, nicardipine, nifedipine, and nimodipine may have their serum concentrations increased by AGENERASE, which could increase their activity.

Cholesterol-Lowering Agents: Atorvastatin, cerivastatin, lovastatin, pravastatin, and simvastatin may have their serum concentration increased by AGENERASE, which could increase their activity or toxicity. Concomitant use of AGENERASE with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including AGENERASE, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir, are used in combination with these drugs.

Erectile Dysfunction Agents: Particular caution should be used when prescribing sildenafil in patients receiving amprenavir. Because amprenavir is a cytochrome P4503A4 inhibitor, coadministration of AGENERASE with sildenafil is likely to result in an increase of sildenafil concentrations by competitive inhibition of metabolism. The magnitude of this interaction has not been determined. Results from drug interaction studies in healthy volunteers indicate that coadministration of saquinavir soft gelatin capsules (1200 mg t.i.d.) increases sildenafil (100-mg single dose) AUC by 210% (3.1-fold) and coadministration of ritonavir (500 mg b.i.d.) increases sildenafil (100-mg single dose) AUC by 1000% (11-fold). Providers should consult the sildenafil prescribing information for dose reductions of sildenafil in patients receiving ritonavir. Patients receiving amprenavir and sildenafil should be advised that they may be at an increased risk for sildenafil-associated adverse events, including hypotension, visual changes, and priapism, and should report these symptoms promptly to their doctor.

NNRTIs: NNRTIs have the potential to increase (delavirdine) or decrease (efavirenz, nevirapine) serum concentrations of amprenavir.

Steroids: Estrogens, progestogens, and some glucocorticoids may have an interaction with AGENERASE, but there is insufficient information to predict the nature of the interaction. Because of this potential for metabolic interactions with amprenavir, the efficacy of hormonal contraceptives may be reduced. Alternate or additional reliable barrier methods of contraception are recommended for women of childbearing potential.

Other Agents: There are other agents that may have their plasma concentrations increased by AGENERASE, and include, but are not limited to: clozapine, carbamazepine, loratadine, pimozide, and warfarin.

Cimetidine and ritonavir may increase amprenavir plasma concentrations.

Antacids (and didanosine secondary to the antacid content) have not been specifically studied. Based upon data with other protease inhibitors, it is advisable that antacids not be taken at the same time as AGENERASE because of potential interference with absorption. It is recommended that their administration be separated by at least an hour.

Use of alcoholic beverages is not recommended in patients treated with AGENERASE Oral Solution.

Carcinogenesis and Mutagenesis: Long-term carcinogenicity studies of amprenavir in rodents are in progress. Amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

Fertility: The effects of amprenavir on fertility and general reproductive performance were investigated in male rats (treated for 28 days before mating at doses producing up to twice the expected clinical exposure based on AUC comparisons) and female rats (treated for 15 days before mating through day 17 of gestation at doses producing up to 2 times the expected clinical exposure). Amprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats. The reproductive performance of the F1 generation born to female rats given amprenavir was not different from control animals.

Pregnancy and Reproduction: AGENERASE Oral Solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content. Therefore, if AGENERASE is used in pregnant women, the AGENERASE Capsules formulation should be used (see complete prescribing information for AGENERASE Capsules).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to AGENERASE, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known if amprenavir is excreted in human milk, amprenavir is

secreted into the milk of lactating rats. Because of both the potential for HIV transmission and any possible adverse effects of amprenavir, **mothers should be instructed not to breastfeed if they are receiving AGENERASE.**

Pediatric Use: AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the excipient propylene glycol (see CONTRAINDICATIONS and WARNINGS). Alcohol dehydrogenase (ADH), which metabolizes propylene glycol, is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12 to 30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

One hundred eighteen patients 4 to 17 years of age have received amprenavir as single or multiple doses in studies. An adverse event profile similar to that seen in adults was seen in pediatric patients.

Geriatric Use: Clinical studies of AGENERASE did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adults. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: Rates of discontinuation of randomized therapy due to adverse events were 15% in amprenavir versus 3% in placebo recipients from Study 3001, and 16% in amprenavir versus 8% in indinavir recipients from Study 3006. In these studies, adverse events leading to amprenavir discontinuation included gastrointestinal events (11%), rash (3%), and paresthesias (<1%).

Most gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain) that led to amprenavir discontinuation were graded as mild or moderate in severity.

In all multidose studies in HIV-infected patients, skin rash occurred in 28% of patients treated with amprenavir. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rashes had onsets ranging from 7 to 73 days (median: 10 days) after amprenavir initiation. With mild or moderate rash, amprenavir dosing was often continued without interruption; if interrupted, reintroduction of amprenavir generally did not result in rash recurrence (Phase 3 studies).

Severe or life-threatening rash, including Stevens-Johnson syndrome, occurred in 1% of recipients of AGENERASE (4% of recipients who developed rash) (see WARNINGS). Amprenavir therapy should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Table 8: Selected Clinical Adverse Events Grades 1-4 (≥5% Frequency)

	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
Adverse Event	AGENERASE*/ Lamivudine/ Zidovudine (n = 113)	Lamivudine/ Zidovudine (n = 109)	AGENERASE*/ NRTI (n = 245)	Indinavir/NRTI (n = 241)
Digestive				
Nausea	73%	50%	38%	26%
Vomiting	29%	17%	20%	11%
Diarrhea or loose stools	33%	34%	56%	32%
Taste disorders	10%	5%	1%	7%
Skin				
Rash	25%	6%	18%	10%
Nervous				
Paresthesia, oral/perioral	26%	5%	30%	2%
Paresthesia (including peripheral)	8%	3%	12%	9%
Psychiatric				
Depressive or mood disorders	15%	4%	4%	6%

*AGENERASE Capsules

In Phase 3 studies, 1 patient experienced diabetes mellitus *de novo*, and another developed a dorsocervical fat enlargement (buffalo hump).

Table 9: Selected Laboratory Abnormalities Grades 1-4 Reported in ≥5% of Patients

Laboratory Abnormality (non-fasting specimens)	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
	AGENERASE*/ Lamivudine/ Zidovudine (n = 113)	Lamivudine/ Zidovudine (n = 109)	AGENERASE*/ NRTI (n = 245)	Indinavir/NRTI (n = 241)
Hyperglycemia (>116 mg/dL)	37%	29%	41%	44%
Hypertriglyceridemia (>213 mg/dL)	36%	22%	47%	40%
Hypercholesterolemia (>283 mg/dL)	4%	3%	9%	10%

*AGENERASE Capsules

In studies 3001 and 3006, no increased frequency of Grade 3 or 4 AST, ALT, amylase, or bilirubin elevations was seen compared to controls.

Pediatric Patients: An adverse event profile similar to that seen in adults was seen in pediatric patients.

OVERDOSAGE: There is no known antidote for AGENERASE. It is not known whether amprenavir can be removed by peritoneal dialysis or hemodialysis. If overdosage occurs, the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary.

AGENERASE Oral Solution contains large amounts of propylene glycol. In the event of overdosage, monitoring and management of acid-base abnormalities is recommended. Propylene glycol can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION: AGENERASE may be taken with or without food; however, a high-fat meal decreases the absorption of amprenavir and should be avoided (see CLINICAL PHARMACOLOGY: Effects of Food on Oral Absorption). **Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content**

of AGENERASE Oral Solution exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU) (see DESCRIPTION).

The recommended dose of AGENERASE Oral Solution based on body weight and age is shown in Table 10. **Consideration should be given to switching patients from AGENERASE Oral Solution to AGENERASE Capsules as soon as they are able to take the capsule formulation (see WARNINGS).**

Table 10: Recommended Dosages of AGENERASE Oral Solution

Age/Weight Criteria	Dose	
	b.i.d.	t.i.d.
4 - 12 years or 13 - 16 years and <50 kg	22.5 mg/kg (1.5 mL/kg) (maximum dose 2800 mg per day)	17 mg/kg (1.1 mL/kg) (maximum dose 2800 mg per day)
13 - 16 years and ≥50 kg or >16 years	1400 mg	NA

Patients with Hepatic Impairment: AGENERASE Oral Solution is contraindicated in patients with hepatic failure (see CONTRAINDICATIONS).

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). AGENERASE Oral Solution should be used with caution in patients with hepatic impairment. Based on a study with AGENERASE Capsules, adult patients with a Child-Pugh score ranging from 5 to 8 should receive a reduced dose of AGENERASE Oral Solution of 513 mg (34 mL) twice daily, and adult patients with a Child-Pugh score ranging from 9 to 12 should receive a reduced dose of AGENERASE Oral Solution of 342 mg (23 mL) twice daily (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency).

AGENERASE Oral Solution has not been studied in children with hepatic impairment.

Renal Insufficiency: AGENERASE Oral Solution is contraindicated in patients with renal failure (see CONTRAINDICATIONS).

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. AGENERASE Oral Solution should be used with caution in patients with renal impairment (see WARNINGS).

AGENERASE Capsules and AGENERASE Oral Solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED:

AGENERASE Oral Solution, a clear, pale yellow to yellow, grape bubblegum-peppermint-flavored liquid, contains 15 mg of amprenavir in each 1 mL.

Bottles of 240 mL with child-resistant closures (NDC 0173-0687-00). This product does not require reconstitution.

Store at controlled room temperature of 25°C (77°F) (see USP).

GlaxoWellcome

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Research Triangle Park, NC 27709

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Cambridge, MA 02139

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US Patent Nos. 5,585,397; 5,723,490; and 5,646,180

Date of Issue RL-no.

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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PATIENT INFORMATION

AGENERASE® (amprenavir) Oral Solution

Please read this information before you start taking AGENERASE (pronounced ah-GEN-er-ase) Oral Solution, and re-read it each time you receive your prescription, just in case something has changed. Remember that this information does not take the place of careful discussions with your doctor when you start this medication and at checkups. You should not change or stop your anti-HIV treatment without first talking with your doctor. **You should tell your doctor about any drug you are taking or planning to take because taking AGENERASE Oral Solution with some medications can result in serious or life-threatening problems.**

What is AGENERASE Oral Solution?

AGENERASE Oral Solution is a medication used to treat HIV infection. HIV is the virus that causes AIDS (acquired immune deficiency syndrome). AGENERASE Oral Solution is taken by mouth as an oral solution. It belongs to a class of anti-HIV medicines called protease inhibitors.

What is the Important Safety Information on AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used in infants and children below the age of 4 years, pregnant women, patients with liver or kidney failure, and patients receiving disulfiram (ANTABUSE®) or metronidazole (FLAGYL®).

AGENERASE Oral Solution contains a large amount of propylene glycol, a liquid needed to dissolve amprenavir. Because of the possible side effects of the large amount of propylene glycol, AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not options. You should not switch from AGENERASE Capsules to AGENERASE Oral Solution without talking to your doctor.

If you are a woman or an Asian, Eskimo, or Native American, or if you have liver or kidney disease, you may be at increased risk of side effects from the large amount of propylene glycol in AGENERASE Oral Solution.

How does AGENERASE Oral Solution work?

AGENERASE Oral Solution is used only in combination with other anti-HIV medicines. When used in combination therapy, AGENERASE Oral Solution may help lower the amount of HIV found in your blood, raise CD4 (T) cell count, and keep your immune system as healthy as possible so that it can help fight infection. However, AGENERASE Oral Solution does not have these effects in all patients.

What are the side effects of AGENERASE Oral Solution?

Common side effects of AGENERASE Oral Solution are nausea, vomiting, diarrhea, rash, and a tingling sensation around the mouth. Severe or life-threatening rash has been reported.

Possible side effects from the large amount of propylene glycol in AGENERASE Oral Solution include seizures, drowsiness, fast heart rate, and kidney and blood abnormalities.

Contact your doctor if you have nausea, vomiting, diarrhea, or rash. Your doctor may be able to help you manage these symptoms. Your doctor will advise you whether your symptoms can be managed on therapy or whether AGENERASE Oral Solution should be stopped.

This list of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of possible side effects with AGENERASE Oral Solution. Talk to your doctor promptly about any side effects you have.

How should I take AGENERASE Oral Solution?

Take AGENERASE Oral Solution exactly as your doctor prescribes it. AGENERASE Oral Solution can be taken with or without food. However, you should not take AGENERASE with a high-fat meal because this could reduce the effectiveness of AGENERASE Oral Solution.

What should I do if I miss a dose of AGENERASE Oral Solution?

To help make sure that your anti-HIV therapy is as effective as possible, be very careful to take all of your medication exactly as your doctor prescribed it and do not skip any doses.

If you miss a dose of AGENERASE Oral Solution by more than 4 hours, wait and take the next dose at the regularly scheduled time. However, if you miss a dose by fewer than 4 hours, take your missed dose immediately. Then take your next dose at the regularly scheduled time. Do not take more or less than your prescribed dose of AGENERASE Oral Solution at any one time.

When your supply of AGENERASE Oral Solution or other anti-HIV drugs starts to run low, arrange to get more from your doctor or pharmacy. It is very important that you take anti-HIV drugs as prescribed by your doctor because the amount of virus in your blood may increase if one or more of the drugs is stopped, even for a short time.

Can AGENERASE Oral Solution be taken with other medications?

Protease inhibitors, including AGENERASE, may interact with other drugs, including those you take without a prescription. Before you take AGENERASE, tell your doctor about any drugs that you are taking or planning to take, including nonprescription drugs.

- **AGENERASE Oral Solution should <u>not</u> be taken with ANTABUSE (disulfiram) or FLAGYL (metronidazole).**

- Drinking alcoholic beverages is not recommended while taking AGENERASE Oral Solution because it may increase side effects related to propylene glycol content.

- **You <u>should not take</u> any of the following medications with AGENERASE Oral Solution because serious or life-threatening problems could occur.***

  HALCION® (triazolam)
  HISMANAL® (astemizole)
  Ergot medications (CAFERGOT® and others)
  PROPULSID® (cisapride)
  VERSED® (midazolam)
  VASCOR® (bepridil)

- **You should also not take rifampin** with AGENERASE Oral Solution because this drug reduces the effectiveness of AGENERASE. Rifampin is also known as: RIFADIN®, RIFAMATE®, RIFATER®, and RIMACTANE®.

- Taking AGENERASE with St. John's Wort (hypericum perforatum, a nonprescription herbal product) or products containing St. John's Wort is not recommended. Talk with your doctor if you are taking or are planning to take St. John's Wort because St. John's Wort may reduce the effect of AGENERASE.

- **Serious and/or life-threatening drug interactions can also occur if you take AGENERASE Oral Solution with any of the following drugs.*** If you need to take any of these drugs, your doctor may closely monitor the amount of drug in your blood to minimize potential problems.
  CORDARONE® (amiodarone)
  Phenobarbital
  DILANTIN® (phenytoin)
  Lidocaine
  COUMADIN® (warfarin)
  (quinidine) QUINAGLUTE®, CARDIOQUIN®, QUINIDEX®
  Antidepressants such as ELAVIL® (amitriptyline), NORPRAMIN® (desipramine), PAMELOR® (nortriptyline), TOFRANIL® (imipramine)

- Tell your doctor about any drugs that you are taking or planning to take, including nonprescription drugs.

- Before you take VIAGRA® (sildenafil) with AGENERASE Oral Solution, talk to your doctor about possible drug interactions and side effects. If you take VIAGRA and AGENERASE Oral Solution together, you may be at increased risk of side effects of VIAGRA such as low blood pressure, visual changes, and penile erection lasting more than 4 hours. If an erection lasts longer than 4 hours, you should seek immediate medical assistance to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you use birth control pills, talk to your doctor about choosing a different type of contraceptive, since AGENERASE Oral Solution may reduce the effectiveness of some birth control pills.

- Because AGENERASE Oral Solution contains large amounts of vitamin E, you should not take additional vitamin E while taking AGENERASE Oral Solution.

- It is not recommended that you take AGENERASE with the cholesterol-lowering drugs MEVACOR® (lovastatin) or ZOCOR® (simvastatin) because of the possible drug interactions. There is also an increased risk of drug interactions between AGENERASE and LIPITOR® (atorvastatin), BAYCOL® (cerivastatin), and PRAVACHOL® (pravastatin). Talk to your doctor if you are taking or are planning to take these or other drugs for lowering cholesterol.

- **Special considerations:***
  If you take AGENERASE Oral Solution with MYCOBUTIN® (rifabutin), your doctor will lower the dose of MYCOBUTIN.
  If you take AGENERASE Oral Solution with VIDEX® (didanosine, ddI), take them at least 1 hour apart.
  If you take AGENERASE Oral Solution with antacids, take them at least 1 hour apart.

Does AGENERASE Oral Solution cure HIV infection or AIDS?

AGENERASE Oral Solution does not cure HIV infection or AIDS. At this time we do not know if AGENERASE will help you live longer or have fewer of the medical problems (opportunistic infections) that are associated with HIV infection or AIDS. Because of this, you must be sure to be seen regularly by your healthcare professional.

Does AGENERASE Oral Solution reduce the risk of passing HIV to others?

No. AGENERASE Oral Solution, as well as other anti-HIV medications, has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

Who should not take AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used in infants and children below 4 years of age, pregnant women, patients with liver or kidney failure, or patients on disulfiram (ANTABUSE) or metronidazole (FLAGYL).

Do not take AGENERASE Oral Solution if you have had a serious allergic reaction to AGENERASE Oral Solution or any of its ingredients. If you have liver disease, your dosage of AGENERASE Oral Solution may have to be adjusted.

If you are allergic to sulfa drugs, you should inform your doctor.

Can children take AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used in infants and children below 4 years of age.

Children from 4 to 12 years of age can take AGENERASE Oral Solution. Your doctor will tell you if the oral solution or capsule is best for your child. Your child's doctor will decide the right dose based on your child's weight and age.

Can pregnant women and nursing mothers take AGENERASE Oral Solution?

AGENERASE Oral Solution should not be used by pregnant women. Talk to your doctor if you are pregnant or if you become pregnant while taking AGENERASE Oral Solution.

Mothers with HIV should not breastfeed their infants because HIV in the breast milk can infect the infant.

What other medical conditions should I discuss with my doctor?

Talk to your doctor if you are pregnant or if you become pregnant while you are taking AGENERASE Oral Solution.

Also talk to your doctor if you have hemophilia or problems with your liver or kidneys.

How should I store AGENERASE Oral Solution?

AGENERASE Oral Solution should be stored at room temperature and should not be refrigerated.

Other information:

This medication is prescribed for a particular condition. Do not use it for any other condition or give it to anybody else. Keep AGENERASE Oral Solution and all medicines out of the reach of children.

Ask a healthcare professional any questions you may have about AGENERASE Oral Solution.

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